Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1543–1546
Tetrahedron Letters

Bismuth triflate catalyzed condensation of δ-hydroxy-α, β-unsaturated aldehydes with aryl amines

J. S. Yadav,* B. V. S. Reddy, G. Parimala and A. Krishnam Raju

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

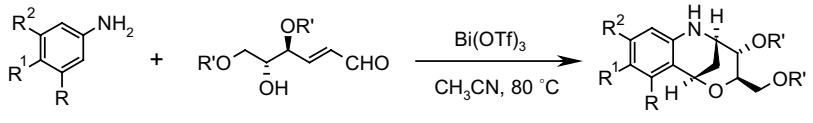
Received 3 September 2003; revised 26 November 2003; accepted 5 December 2003

Abstract—α,β-Unsaturated aldehydes bearing a δ-hydroxyl group undergo a tandem Michael and intramolecular Friedel–Crafts type cyclization with arylamines in the presence of 5 mol% of $Bi(OTf)_3$ under mild conditions to afford a new class of chiral tetrahydroquinolines in good yields with high stereoselectivity. Structural assignments and the stereochemistry of the products was achieved using various 1D and 2D-NMR experiments.

The tetrahydroquinoline moiety is a core structure in various natural products and synthetic pharmaceuticals.[1] The pyranoquinoline framework is present in many alkaloids[2] such as flindersine, oricine and veprisine and derivatives of these alkaloids possess a wide range of biological activities such as psychotropic, antiallergic, anti-inflammatory and estrogenic activities.[3] High catalytic activity, low toxicity, moisture and air tolerance and their recyclability make lanthanide triflates attractive alternatives to conventional Lewis acids.[4] Recently, bismuth triflate has evolved as a remarkable Lewis acid catalyst for effecting various organic transformations.[5] Compared to lanthanide triflates, bismuth triflate is inexpensive and easy to prepare even on multi-gram scale in the laboratory from commercially available bismuth oxide and triflic acid.[6]

In this report, we describe a novel route for the synthesis of enantiopure tetrahydroquinolines in a one-pot operation using a catalytic amount of bismuth triflate under mild conditions (Scheme 1).

Thus treatment of enantiopure 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose[7] **2a** with aniline in the presence of 5 mol% of $Bi(OTf)_3$ in acetonitrile at 80 °C afforded tetrahydroquinoline **3a** in 80% yield.[8] The product **3a** was characterized by using various NMR experiments such as double quantum filtered correlation spectroscopy (DQFCOSY), nuclear Overhauser effect spectroscopy (NOESY), hetero nuclear single quantum correlation spectroscopy (HSQC) and $^3J_{CH}$ optimized HMBC experiments. The edited HSQC spectrum showed the presence of two methylene groups



1 2 R' = Ac, Me, Bn 3

Scheme 1.

Keywords: Arylamines; Bismuth reagents; Unsaturated aldehydes; Heterobicycles.
* Corresponding author. Tel.: +91-402-7193434; fax: +91-40-27160512; e-mail: yadav@iict.ap.nic.in

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.043

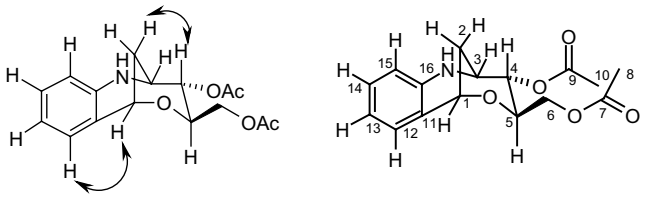


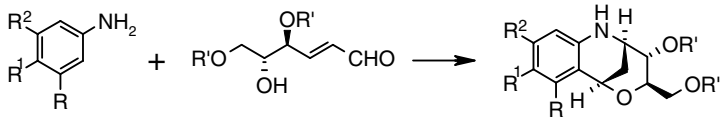
Figure 1. NOEs and chemical structure of **3a**.

in addition to eight methine and two methyl groups. The location of a methylene on the bridge of the bicyclononene like structure was confirmed by the presence of small couplings between the bridge protons H_2 and the bridgehead protons H_1 and H_3 $J_{1H-2H} = 3.7$ Hz, $J_{1H-2H} = 1.8$ Hz, $J_{2H-3H} = 2.4$ Hz, and $J_{2H-3H} = 4.6$ Hz. Fusion of the bicyclononene and the aromatic ring at C_{11}–NH was confirmed by an NOE between H_1 and H_{12}. Further support for the structure came from HMBC peaks between H_1–C_{12}, H_1–C_{11}, H_1–C_{16} and H_{12}–C_1. The two six-membered rings of the bicyclononene moiety have two different conformations. The one containing oxygen takes a chair form whereas the other ring with nitrogen and fused to the aromatic ring exists in a half chair form. HMBC peaks between H_2–C_{11} and H_2–C_4 are consistent with the structure. The large coupling constant value of $J_{H4-H5} = 10.4$ Hz and the NOESY cross peak between H_2–H_4 further support the chair form for the ring containing these protons. The ring current effect due to the aromatic ring causes high field chemical shifts of H_2 ($\delta = 1.96$ ppm) and H_5 ($\delta = 3.58$ ppm) (Fig. 1).

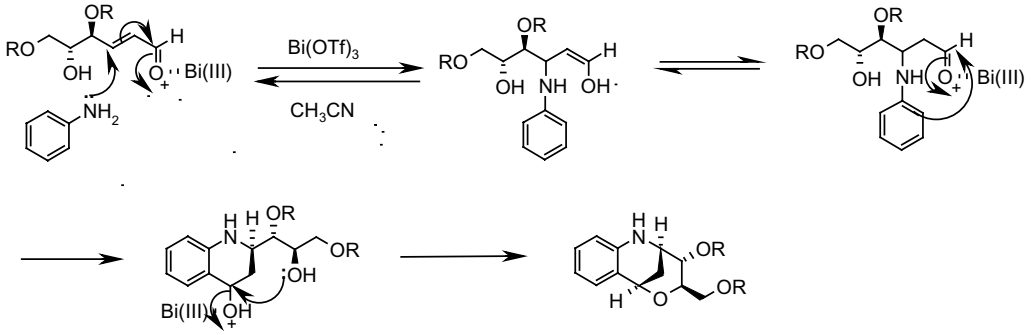
Encouraged by the results obtained with aniline, we turned our attention towards various arylamines and δ-hydroxy-α,β-unsaturated aldehydes. Interestingly, a variety of aryl amines including mono-, di- and trisubstituted anilines reacted efficiently with 2a under similar conditions to afford the corresponding benzo-fused heterobicycles in fairly good yields. Other substituted δ-hydroxy-α,β-unsaturated aldehydes such as methoxy- and benzyloxy derivatives also gave similar results (entries **n** and **o**, Table 1). However, *ortho*-hydroxy *trans*-cinnamaldehyde and aniline did not give the desired product under the reaction conditions. Furthermore, simple α,β-unsaturated aldehydes without a δ-hydroxyl group did not yield a bicyclic adduct. The reaction proceeded only with δ-hydroxy-α,β-unsaturated aldehydes. The probable mechanism seems to be the addition of the aniline to the unsaturated position of the conjugated aldehyde, which is activated by the bismuth triflate. Thus the initially formed Michael adduct may undergo a Friedel–Crafts type intramolecular cyclization leading to the formation of the chiral tetrahydroquinoline (Scheme 2).

The method is highly stereoselective affording novel heterobicycles under mild reaction conditions. The efficacy of various metal triflates such as $In(OTf)_3$, $Ce(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $Bi(OTf)_3$ was studied for this conversion. Among the various metal triflates, $Bi(OTf)_3$ was found to be the most effective catalyst in terms of conversion. For instance, treatment of 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose **2a** with aniline in the presence of 5 mol% $Bi(OTf)_3$ and 5 mol% $In(OTf)_3$ for 3 h afforded 80% and 65% yields, respectively. The scope and generality of this process is illustrated with respect to various aryl amines and α,β-unsaturated aldehydes and the results are presented in Table 1.[9] It is important to mention that this

Table 1. $Bi(OTf)_3$-catalyzed synthesis of benzo-fused heterobicycles

Entry	Aryl amine	α,β-unsaturated aldehyde	Product[a]	Reaction time (h)	Yield (%)[b]
					
1a	$R = R^1 = R^2 = H$	$R' = Ac$	**3a**	5.0	80
1b	$R = Me$; $R^1 = R^2 = H$	$R' = Ac$	**3b**	4.0	86
1c	$R = R^1 = H$; $R^2 = F$	$R' = Ac$	**3c**	6.0	79
1d	$R = R^1 = H$; $R^2 = Cl$	$R' = Ac$	**3d**	5.0	85
1e	$R = R^2 = Cl$; $R^1 = H$	$R' = Ac$	**3e**	6.0	80
1f	$R = R^2 = H$; $R^1 = Me$	$R' = Ac$	**3f**	5.0	83[c]
1g	$R = H$; $R^1 = Cl$; $R^2 = F$	$R' = Ac$	**3g**	6.5	78
1h	$R = R^1 = H$; $R^2 = Ph$	$R' = Ac$	**3h**	6.0	82
1i	$R = CN$; $R^1 = R^2 = H$	$R' = Ac$	**3i**	7.0	70
1j	$R = R^2 = F$; $R^1 = H$	$R' = Ac$	**3j**	6.5	75
1k	$R = R^1 = H$; $R^2 = Br$	$R' = Ac$	**3k**	6.0	80
1l	$R = R^1 = H$; $R^2 = Me$	$R' = Ac$	**3l**	4.5	85
1m	$R = Br$; $R^1 = H$; $R^2 = Me$	$R' = Ac$	**3m**	5.5	77
1n	$R = R^1 = R^2 = H$;	$R' = Me$	**3n**	5.0	79
1o	$R = R^1 = H = R^2 = H$	$R' = Bn$	**3o**	6.0	72

[a] Products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] Regioisomeric ratio (7:3) determined by ^1H NMR.



Scheme 2.

procedure works well only with aryl amines and is not suitable for alkyl amines.

In summary, we disclose a novel protocol for the synthesis of sugar derived chiral tetrahydroquinolines from δ-hydroxy-α,β-unsaturated aldehydes and aryl amines using a catalytic amount of $Bi(OTf)_3$ under mild reaction conditions. This method is quite simple and straightforward and constructs unusual benzo-fused heterobicycles in a single-step operation.

Acknowledgements

B.V.S. and A.K.R. thank CSIR New Delhi, for the award of fellowships.

References and notes

1. (a) Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987, Chapters 2 and 9; (b) Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
2. (a) Ramesh, M.; Mohan, P. A.; Shanmugam, P. *Tetrahedron* **1984**, *40*, 4041–4049; (b) Jurd, L.; Wong, R. V. *Aust. J. Chem.* **1981**, *34*, 1625–1632; (c) Coppola, G. M. *J. Heterocycl. Chem.* **1983**, *20*, 1217–1221.
3. (a) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211; (b) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177–1178; (c) Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949.
4. (a) Kobayashi, S. *Synlett* **1994**, 689–701; (b) Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 370; (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27.
5. Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397.
6. Repichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993–995.
7. The acyclic α,β-unsaturated aldehydes were prepared from D-glucal using a procedure reported in the literature: Wengel, J.; Lau, J.; Pedersen, E. B. *Synthesis* **1989**, 829–831.
8. The product **3a** was also obtained from glucal triacetate and aniline: see Ref. Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Saritha Raj, K.; Prasad, A. R.; Kiran Kumar, S.; Kunwar, A. C.; Jayaprakash, P.; Jagannadh, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5198–5201.
9. Representative experimental procedure: A mixture of 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro-trans*-hex-2-enose (1 mmol), the arylamine (1.5 mmol) and $Bi(OTf)_3$ (0.05 mmol) in acetonitrile (10 mL) was stirred at 80 °C for the appropriate time (Table). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure benzo-fused heterobicycle. Spectral data for selected products: **3a**: Liquid, $[\alpha]_D^{25}$ 95.5° ($c = 1.0$, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (dt, $J = 1.5$, 7.9 1H, H13), 7.13 (dd, $J = 1.5$, 7.9 1H, H15), 6.69 (dt, $J = 1.5$, 7.9, 1H, H14), 6.61 (dd, $J = 1.5$, 7.9, 1H, H12), 4.84 (dd, $J = 3.1$, 10.4, 1H, H4), 4.81 (dd, $J = 1.8$, 3.7, 1H, H1), 4.44 (br s, 1H, NH), 4.19 (dd, $J = 4.2$, 12.0, 1H, H6), 3.99 (dd, $J = 2.2$, 12.0, 1H, H6′), 3.84 (ddd, $J = 2.4$, 3.1, 4.6, 1H, H3), 3.58 (ddd, $J = 2.1$, 4.2, 10.4, 1H, H5), 2.29 (ddd, $J = 2.4$, 3.7, 13.2, 1H, $H2_{pro\text{-}R}$), 2.10 (s, 3H, CH_3-10), 2.06 (s, 3H, CH_3-8), 1.96 (ddd, $J = 1.8$, 4.6, 13.2, 1H, $H2_{pro\text{-}S}$). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8 (C7), 169.8 (C9), 145.0 (C11), 130.5 (C15), 129.9 (C13), 118.8 (C16), 117.2 (C14), 112.9 (C12), 71.8 (C4), 68.5 (C1), 67.4 (C5), 63.0 (C6), 46.6 (C3), 27.9 (C2), 21.0 (C10), 20.7 (C8). IR (KBr): ν_{max}: 3427, 2935, 2857, 1730, 1607, 1461, 1365, 1257, 1098, 835 cm^{-1}. FAB Mass: 305M,$^+$ 259, 191, 144, 130, 119, 91, 69, 57. HRMS calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1275. **3b**: Liquid, $[\alpha]_D^{25}$ 83.7° ($c = 0.8$, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 6.98–6.95 (m, 2H), 6.60 (t, $J = 7.9$ Hz, 1H,), 4.82 (dd, $J = 3.2$, 10.5 Hz, 1H), 4.78 (dd, $J = 1.7$, 3.8 Hz, 1H), 4.22 (dd, $J = 4.2$, 12.0, 1H), 4.20 (br s, 1H, NH), 3.95 (dd, $J = 2.1$, 12.0, 1H), 3.90 (ddd, $J = 2.4$, 3.2, 4.5 Hz 1H), 3.55 (ddd, $J = 2.1$, 4.2, 10.5 Hz, 1H), 2.30 (ddd, $J = 2.4$, 3.7, 13.0 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.95 (ddd, $J = 1.7$, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.9, 169.9, 143.0, 130.8, 128.4, 120.1, 118.4, 116.8, 71.7, 68.8, 67.3, 63.1, 46.9, 29.6, 27.9, 21.0, 20.8. IR (KBr): ν_{max}: 3422, 2931, 2858, 1734, 1604, 1472, 1367, 1254, 1093, 837 cm^{-1}. FAB Mass: 319 M,$^+$ 281, 207, 158, 144, 105, 91, 73, 57. HRMS calcd for $C_{17}H_{21}NO_5$: 319.1419. Found: 319.1427. **3c**: Liquid, $[\alpha]_D^{25}$ 67.1° ($c = 0.75$, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 6.78–6.90 (m, 2H), 6.45–6.50 (m, 1H), 4.80 (dd, $J = 3.1$, 10.5 Hz, 1H), 4.70 (dd, $J = 1.8$, 3.8 Hz, 1H), 4.30 (br s, 1H, NH), 4.20 (dd, $J = 4.2$, 12.0 Hz, 1H), 3.90 (dd,

$J = 2.1$, 12.0 Hz, 1H), 3.80 (ddd, $J = 2.5$, 3.1, 4.5 Hz, 1H), 3.50 (ddd, $J = 2.1$, 4.2, 10.3 Hz, 1H), 2.25 (ddd, $J = 2.5$, 3.8, 13.1 Hz, 1H), 2.10 (s, 3H), 2.0 (s, 3H), 1.95 (ddd, $J = 1.8$, 4.5, 13.1 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.3, 169.4, 156.9, 141.1, 119.6, 117.2, 116.9, 113.9, 71.7, 68.1, 67.7, 62.9, 46.7, 27.9, 21.0, 20.8. IR (KBr): ν_{max}: 3356, 2961, 1733, 1505, 1260, 1040, 809 cm^{-1}. FAB Mass: 323 M,$^+$ 267, 221, 191, 147, 133, 73. HRMS calcd for $C_{16}H_{18}FNO_5$: 323.1169. Found: 323.1157. **3k**: Liquid, $[\alpha]_D^{25}$ 169.2° ($c = 1.5$, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10–7.20 (m, 2H), 6.50 (d, 1H, $J = 8.1$ Hz), 4.80 (dd, $J = 3.2$, 10.5 Hz, 1H), 4.70 (dd, $J = 1.8$, 3.8 Hz, 1H), 4.40 (br s, 1H, NH), 4.25 (dd, $J = 4.2$, 12.0 Hz, 1H), 4.10 (dd, $J = 2.1$, 12.0 Hz, 1H), 3.90 (ddd, $J = 2.5$, 3.2, 4.5 Hz, 1H), 3.80 (ddd, $J = 2.1$, 4.2, 10.3 Hz, 1H), 2.30 (ddd, $J = 2.5$, 3.8, 13.0 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.90 (ddd, $J = 1.8$, 4.5, 13.0 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.8, 169.8, 143.9, 132.8, 132.6, 129.1, 120.6, 114.6, 71.5, 68.0, 67.5, 62.9, 46.5, 27.5, 20.9, 20.7. IR (KBr): ν_{max}: 3410, 3019, 2955, 1738, 1603, 1490, 1371, 1246, 1046, 813, 757 cm^{-1}. FAB: Mass: 383 M,$^+$ 368, 340, 327, 289, 265, 239, 224, 219, 191, 165. HRMS calcd for $C_{16}H_{18}BrNO_5$: 383.0368. Found: 383.0373.